REMARKS

Applicants appreciate the Examiner's time and guidance during the interview that was held at the U.S. Patent and Trademark Office on October 25, 2001. The remarks that follow, and the data presented to establish surprising results, are consistent with that discussion.

The pending claims

Claims 54, 57-59, 61-69, and 88-124 are now pending in the present application, claims 70-87 having been cancelled by the present amendment and claims 88-124 having been added. As claims 70-87 have already been examined, Applicants wish to point out that, although those claims have been cancelled, the subject matter they covered remains in the application. Those cancelled claims (70-87) are essentially renumbered, with additional claims interspersed, so that the claim set, as a whole, is more clearly organized. The subject matter previously claimed in claim 70 now appears in new **claim 92**; that of cancelled claim 71 now appears in new **claim 93**; that of cancelled claim 72 now appears in new **claim 94**; that of cancelled claim 73 now appears in new **claim 95**; that of cancelled claim 74 now appears in new **claim 96**; that of cancelled claim 75 now appears in new **claim 99**; that of cancelled claim 76 now appears in new **claim 100**; that of cancelled claim 77 now appears in new **claim 101**; that of cancelled claim 78 now appears in new **claim 102**; that of cancelled claim 79 now appears in new **claim 105**; that of cancelled claim 80 now appears in new **claim 106**; that of cancelled claim 81 now appears in new **claim 107**; that of cancelled claim 82 now appears in new **claim 108**; that of cancelled claim 83 now appears in new **claim 109**; that of cancelled claim 84 now appears in new **claim 110**; that of cancelled claim 85 now appears in new **claim 111**; that of cancelled claim 86 now appears in new **claim 114**; and that of cancelled claim 87 now appears in new **claim 123**. New **claims 88-91, 97-98, 103-104, 112-113. and 119-120**, which further limit the type of cell mediated immune response, are supported by the specification at, for example, page 14, lines 15-19. New **claims 115-118, 121-122, and 125** cover methods of preventing or treating an HPV infection in a mammal. These claims parallel those covering methods of inducing an immune response against an antigen of an influenza virus (see, *e.g.*, claims 64-67), and they are supported throughout the specification at, for example, page 19, lines 3-8 and 24-31, page 30, lines 16-18, page 31, lines 4-9 and the Examples at pages 34-52. No new matter has been added.

35 U.S.C. § 103

A. The rejection with respect to stress proteins and *influenza* antigens

Claims 54, 57, 59, 61-65 and 68-74 are rejected as being obvious over Young (WO 94/29459) in view of Smith *et al.* (U.S. Patent No. 5,858,368; herein, "Smith") (Office Action at page 2). This ground for rejection is respectfully traversed.

The Examiner begins by summarizing Young and Smith. More specifically, the Examiner states that Young discloses "fusion proteins of bacterial stress proteins with antigens, proteins or peptides," and, according to Young, heat shock proteins (hsps) are known to induce T-cell mediated immune responses (Office Action at page 2). Moreover, hsps can be produced recombinantly (and can be produced recombinantly in fusion with an antigen) (Office Action at page 3). Young exemplifies a fusion protein between hsp70 and HIV p24 antigen, which induced a humoral response to p24 that was more than two-fold greater than the response to p24 alone (Office Action at page 3). The Examiner recognizes that Young does not disclose influenza antigens (Office Action at page 3).[1]

To supply the missing limitation (influenza antigens), the Examiner turns to Smith, who discloses recombinant fusion proteins that include influenza hemagglutinin (HA) and a heterologous sequence (preferably, a baculovirus signal sequence in lieu of the HA signal sequence) (Office Action at page 3). The Examiner notes that Smith's fusion proteins are easier to produce, and they elicit a protective humoral response (Office Action at page 3).

Given these disclosures, the Examiner concludes that it would have been obvious to one of ordinary skill in the art to have replaced the p24 antigen in Young's hsp70-p24 fusion with Smith's influenza antigen (HA), thereby creating an hsp70-HA fusion protein that would fall within the scope of the present claims (Office Action at page 3). The Examiner finds that one would have been motivated to provoke both humoral and cellular immune responses, since most effective vaccines activate both parts of the immune system, and would have had a reasonable expectation of success because only routine cloning skills would be required (Office Action at page 3).

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[1] To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the limitations of a claim. MPEP at 2142.

The present claims are patentable because it was not obvious to select an influenza antigen as a component of the fusion protein.

Fusion proteins containing stress proteins are known in the art (*see, e.g.*, Young).[2] But this does not mean that all fusion proteins containing stress proteins are obvious. The genus-species relationship was addressed in view of the statutory requirement for non-obviousness in *In Re Baird*, 16 F.3d 380 (Fed. Cir. 1994). As discussed during the interview, the facts in the present case are consistent with those in *Baird*, and here, as in *Baird*, there is patentable subject matter.

Baird claimed a toner comprising a binder resin; the binder resin was a bisphenol A polyester, which could contain succinic acid, glutaric acid, or adipic acid. Baird's claims were rejected as being obvious over a single piece of prior art: a U.S. patent to Knapp, which disclosed "developer compositions" comprising a diphenol having a generic formula. Knapp also taught that succinic acid, glutaric acid, and adipic acid could be included. The Examiner argued that Baird's claims to bisphenol A were obvious because bisphenol A is produced when certain specific variables are selected for inclusion in Knapp's generic formula. The Examiner argued that bisphenol A could be easily derived from Knapp's generic formula, particularly since Knapp also described the required elements (succinic, glutaric, and adipic acid). The Board of Appeals and Patent Interferences affirmed the Examiner's rejection. Nevertheless, the Court of Appeals for the Federal Circuit found Baird's claims were non-obvious. The court found nothing in Knapp to suggest that one should ***select*** the variables required to produce bisphenol A.

The facts in the present case parallel those in *Baird*, and the conclusion here should be the same as that in *Baird*: non-obviousness. In fact, certain aspects of the present case provide an even stronger basis for this outcome. For example, in *Baird* both the generic formula and the specific variables that, if chosen, would give rise to the compound claimed, were found within a single prior art reference (the Knapp patent). Here, one of ordinary skill in the art would have to look beyond Young, which fails to mention influenza antigens or HPV antigens at all. The invention Baird claimed was found non-obvious because there was no suggestion in Knapp to

[2] Many stress proteins are induced in response to heat and are, therefore, also known as hsps.

select bisphenol A from the vast number of diphenols covered by the generic formula. The present Applicants make the same argument: there is no suggestion in Young, or in the combination of Young and Smith, to select an influenza antigen from the vast number of antigens that could be included in a stress protein-containing fusion protein. In accordance with the law on obviousness, this ground for rejection should be withdrawn.

There is no motivation to combine Young and Smith.

As the Examiner appreciates, for *prima facie* obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. MPEP at 2142. As noted above, the Examiner finds that one would have been motivated to replace Young's HIV antigen (p24) with Smith's influenza antigen (HA) to provoke both humoral and cellular immune responses. Applicants respectfully disagree.

Smith discloses a *method* in which insect cells are used to prepare an influenza antigen (or antigens) for inclusion in a vaccine. The baculovirus expression system *per se* is an important part of Smith's contribution to the art, as it allows one to prepare the antigenic component of a vaccine from primary sources of influenza (*e.g.*, nasal secretions from patients who have the flu), rather than from virus that is adapted to, and cultured in, chicken eggs (see the abstract and column 4, lines 17-25 (4:17-25)). To practice his method, Smith did make a fusion construct, but it is not one that could possibly suggest the fusion Applicants now claim. Smith teaches (at 3:62 – 4:6; emphasis added):

> In a preferred embodiment, the cloned HA genes are modified by *deletion of* the nucleotides encoding the natural hydrophobic signal peptide sequences and *replacement with a new baculovirus signal peptide* to yield a sequence encoding the signal peptide immediately abutting the hemagglutinin. These chimeric genes are introduced into baculovirus expression vectors so that the baculovirus polyhedrin promoter directs the expression of recombinant HA proteins in infected insect cells. The 18 amino acid *baculovirus signal peptide* directs the translation of rHA into the insect cell glycosylation pathway and *is not present on the mature rHA glycoprotein.*

Thus, in Smith's fusion, the natural signal sequence for the antigen of interest is replaced by a signal sequence appropriate for -- and dictated by -- the expression system used. Upon

expression, the signal peptide is cleaved off. Only the influenza antigen(s) appear in Smith's final product (these antigens, which may also be fused, are discussed further below). Nothing about Smith's method suggests fusion between an influenza antigen and a stress protein. Indeed, a stress protein could not function as a signal sequence.

Moreover, the results Smith obtained with his influenza antigen were very good. In Example 8, Smith establishes that his rHA antigen was at least as good as a commercially available influenza vaccine and, with alum, Smith's rHA elicits IgG HA antibodies that are higher than the commercial vaccine. If Smith's vaccine is "well-tolerated and capable of eliciting *protective* immune responses in human subjects" (27:64-66; emphasis added), there is little or no motivation to modify it. The fact that some vaccines stimulate both arms of the immune system, is not enough. Furthermore, although Smith characterized only the humoral response, he clearly suggests that his vaccine can elicit both humoral and cellular immune responses. Smith teaches that, in some circumstances, it may be desirable to fuse HAO to a second antigenic protein, and the immune response that results is defined as "either a *humoral response*, measured by the production of antibody to the antigen, or a *cellular response*, measured by the elicitation of a T cell mediated response to the antigen" (12:41-43; emphasis added). But the second antigenic protein is *not* a stress protein. In fact, Smith would lead one away from inclusion of a stress protein. Smith states (at 12:32-35; emphasis added):

> Fusion proteins consisting of the HAO fused to a second antigenic protein can be made where the antigenicity of the second protein is *low* or there are *advantages* to eliciting an immunogenic response to multiple antigens. An example of a preferred second antigen is the neuraminidase produced by influenza.

There is no motivation to select a stress protein because the antigenicity of stress protein is *not low* and there is *no advantage* to eliciting an immunogenic response to a stress protein in the context of an influenza vaccine. What one *would* select to treat influenza is another influenza antigen (Smith suggests neuraminidase). There is no motivation in the citied references, considered alone or in combination, to make the fusion protein now claimed. As such motivation is required for *prima facie* obviousness, this ground for rejection should be withdrawn.

B. The rejection with respect to stress proteins and *human papilloma virus* (HPV) antigens

Claims 75-87 were rejected as being obvious over Young in view of Lathe *et al.* (U.S. Patent No. 6,007,806; herein, "Lathe"). As noted above, claims 75-87 have been cancelled, but the subject matter they covered is now covered in new claims 99-102, 105-111, 114, and 123, respectively. This ground for rejection is respectfully traversed.

The Examiner's characterization of Young is as summarized above (see also, Office Action at page 4). The Examiner recognizes that Young fails to disclose HPV antigens and, accordingly, turns to Lathe. More specifically, the Examiner notes that Lathe "discloses recombinant fusion proteins wherein HPV antigens are recombinantly produced for use in a vaccine against HPV-induced tumors" (Office Action at page 4). The HPV antigens E6 and E7 are disclosed, and are said to be useful in treating or preventing tumors of HPV origin (Office Action at page 4).

Given these disclosures, the Examiner concludes that it would have been obvious to one of ordinary skill in the art to have replaced the p24 antigen in Young's hsp70-p24 fusion with Lathe's HPV E6 or E7 antigen, thereby creating an hsp70-E6 or hsp70-E7 fusion protein that would fall within the scope of the present claims (Office Action at page 5). The Examiner finds that one would have been motivated to provoke both humoral and cellular immune responses, since most effective vaccines activate both parts of the immune system, and would have had a reasonable expectation of success because only routine cloning skills would be required (Office Action at page 5).

It was not obvious to select an HPV antigen for inclusion in a fusion protein.

The remarks above concerning the law of obviousness established in *In re Baird* are applicable to Applicants' claims covering stress protein-HPV fusion proteins. The Examiner is asked to consider those remarks with full force with respect to these claims. Stress protein-containing fusion proteins, broadly disclosed by Young, cannot render obvious the specific stress protein-HPV fusions now claimed.

There is no motivation to combine Young with Lathe

Lathe uses vaccinia viral vectors to induce an immune response. Notably, antigens expressed by those vectors induce a cellular immune response. This is well known in the art and taught by Lathe. For example, Lathe states (2:42-67; emphasis added):

> The use of vaccinia virus as cloning and expression vector for foreign antigens has already been described [citations omitted]. Recombinant viruses expressing antigens of heterologous viruses or of parasites have been employed to immunize animals against the corresponding pathogen [citation omitted]. The antigens expressed by recombinant vaccinia virus are presented in the appropriate manner on the surface of infected cells *and they enable a cell-type immune response to be induced* [citations omitted], which is particularly advantageous because it is known that the removal of tumor cells involves cellular immunity [citations omitted].

By stating that the "regression and/or prevention of HPV tumors [observed by Lathe] shows that E6 and E7 are each able to activate immune effector cells necessary for the elimination and/or prevention of the tumor cells," the Examiner appears to recognize that Lathe has induced a cellular immune response. Accordingly, there is no motivation to modify an HPV antigen to achieve such a response, let alone to modify the antigen by fusion to a stress protein. On this basis alone, the rejection for obviousness should be withdrawn.

Even if there were a *prima facie* case of obviousness, Applicants have surprising results

Applicants have now tested a fusion protein designated HspE7 (Hsp65 from *Mycobacterium bovis* variant BCG and the E7 antigen of HPV, type 16) in clinical trials with human patients suffering from anal dysplasia. The remarks below are supported by the Declaration of Dr. Lee Mizzen (Tab A; herein, "Mizzen Declaration").

Patients who had persistent anal high-grade squamous intraepithelial lesions (HSIL) were studied. Anogenital warts were not a trial parameter, but a retrospective review of the medical records of the first 22 patients enrolled at one site was undertaken to estimate the quality and frequency of responses of anogenital warts. The patients were typed for HPV by PCR assays using cells obtained from an anal swab, but the patients were not required to score positive for HPV type 16 (HPV16) to be enrolled in the study (Mizzen Declaration at ¶ 3).

Patients received three subcutaneous injections of either 100 μg of HspE7 or placebo at monthly intervals. They were assessed for treatment response by anal Pap smears, high-resolution anoscopy (HRA) with biopsy, and global physician assessment. Non-responders (*i.e.*, patients with persistent anal HSIL) after 12 or 24 weeks in the controlled trial were allowed to crossover to an open-label trial where they received three injections of 500 μg of HspE7 at monthly intervals (Mizzen Declaration at ¶ 4).

At the time of their entry into the open-label trial, 14 of the 22 patients (64%) had persistent anogenital warts. One month after the final treatment with 500 μg of HspE7, two patients (14%) had no detectable warts, 11 patients (79%) had a reduction in the size or number of warts (relative to the size or number at the beginning of the open-label trial), and one patient (7%) experienced an increase in wart size. Four months after the final dose of HspE7, one additional patient experienced an improvement from partial to complete response (characterized as having no visible warts), giving a total of three (21%) complete responders. None of these responders experienced a relapse during the six-month evaluation period (Mizzen Declaration at ¶ 5).

In all 14 patients diagnosed with anogenital warts, DNA of multiple HPV types was detected in anal swab specimens. Most patients whose warts improved (85%) were not HPV16 positive. HPV types 6 and/or 11 were frequently detected. These data suggest that patients infected with HPV other than type 16 can respond to HspE7 treatment, and that anogenital warts, which are commonly associated with HPV types 6 and 11, can be treated by HspE7. This is surprising and beneficial. Many patients are infected with multiple types of HPV, indicating that infection with one HPV type does not provide protection against subsequent infection with a second HPV type. Thus, one would not have expected administration of an immunotherapeutic agent containing an antigen from a single HPV type (here, the E7 protein of HPV16) would benefit patients infected with other HPV types (*i.e.*, non-HPV16). One of the benefits of this unexpected result is that Applicants' immunotherapeutic agent (HspE7) can be used to treat diseases caused by different HPV types (here, anal HSIL and anogenital warts). Therefore, it may not be necessary to develop separate therapies for each HPV type as was previously thought. Accordingly, with a single therapeutic agent, HspE7, a greater number of patients with

different manifestations of HPV infection (*e.g.* dysplasia and warts) can be treated (Mizzen Declaration at ¶ 6).

In view of this evidence of unexpected results, the Examiner is asked to reconsider and withdraw the rejection for obviousness.

CONCLUDING REMARKS

As the amendment only adds new claims, no marked-up version of the changes is included. Enclosed is a Petition for Extension of Time and a second check for the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: February 25, 2002

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